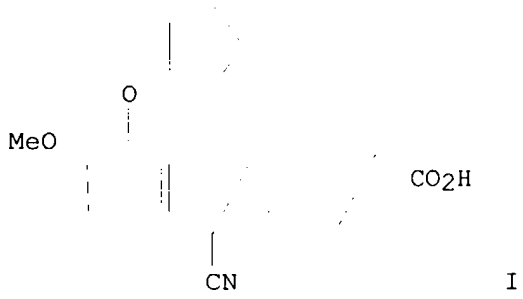
=> d ibib abs hitstr l12 1-2

L12 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:830855 HCAPLUS
DOCUMENT NUMBER: 138:73055
TITLE: A Practical Synthesis of the PDE4 Inhibitor, SB-207499, from a Cyclohexanone Precursor
AUTHOR(S): Badham, Neil F.; Chen, Jian-Hao; Cummings, Paul G.; Dell'Orco, Philip C.; Diederich, Ann M.; Eldridge, Ann M.; Mendelson, Wilford L.; Mills, Robert J.; Novack, Vance J.; Olsen, Mark A.; Rustum, Abu M.; Webb, Kevin S.; Yang, Shawn
CORPORATE SOURCE: Department of Synthetic Chemistry, GlaxoSmithKline Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Organic Process Research & Development (2003), 7(1), 101-108
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:73055
GI

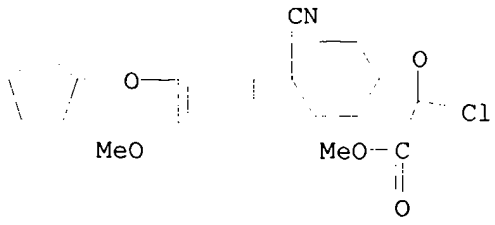


I

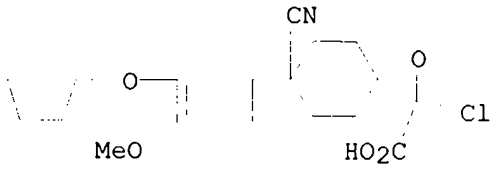
AB The synthesis of SB-207499 (I) is described. Investigation and development of new strategies for the homologation of 4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexanone are described which produce I. Our ultimate route to I is robust and operationally simple and produces the final drug substance in good yield and purity.

IT **326008-99-5P 326009-00-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of PDE4 inhibitor SB-207499 from cyclohexanone precursor)

RN 326008-99-5 HCAPLUS
CN 1-Oxaspiro[2.5]octane-2-carboxylic acid, 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-, methyl ester (9CI) (CA INDEX NAME)



RN 326009-00-1 HCAPLUS
CN 1-Oxaspiro[2.5]octane-2-carboxylic acid, 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:115107 HCAPLUS
DOCUMENT NUMBER: 134:178271
TITLE: Process for preparing substituted cyclohexanoic acids via α-chloroepoxy esters
INVENTOR(S): Diederich, Ann M.; Novak, Vance J. Applicant
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001010822	A1	20010215	WO 2000-US21394	20000804
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CZ, DZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000013025	A	20020416	BR 2000-13025	20000804
EP 1200394	A1	20020502	EP 2000-953844	20000804
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003506431	T2	20030218	JP 2001-515289	20000804
ZA 2002000965	A	20030204	ZA 2002-965	20020204
NO 2002000561	A	20020205	NO 2002-561	20020205

PRIORITY APPLN. INFO.: US 1999-147576P P 19990806
WO 2000-US21394 W 20000804

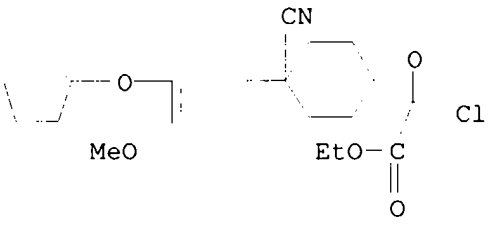
OTHER SOURCE(S): CASREACT 134:178271; MARPAT 134:178271
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A process for preparing substituted cyclohexanoic acids I is proposed, where Ra is a carbon-containing group optionally linked by oxygen, sulfur or nitrogen to the cyclohexyl ring and n is 1-10; and R and R* are independently but not simultaneously hydrogen or C(O)E where E is OR14 or SR14, where R14 is hydrogen or alkyl of 1-6 carbon atoms; which process comprises treating an epoxide II with DMSO and an alkali metal salt, wherein E is OR14 or SR14, where R14 is hydrogen or alkyl of 1-6 carbon atoms; Ra is the same as defined for I; and Y is Br, Cl, F or I. Thus, α-chloroepoxy ester III was prepared via reaction of 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one with Me dichloroacetate and tert-butoxide in THF, subsequently saponified and the corresponding chloroepoxy acid treated with DMSO, NaCl and water, and heated to 150 °C for 3.5 h to yield IV (59%).

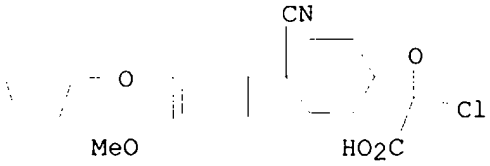
IT **326009-01-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing substituted cyclohexanoic acids via α-chloroepoxy esters)

RN 326009-01-2 HCAPLUS
CN 1-Oxaspiro[2.5]octane-2-carboxylic acid, 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-, ethyl ester (9CI) (CA INDEX NAME)



IT **326009-00-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for preparing substituted cyclohexanoic via α-chloroepoxy esters)

RN 326009-00-1 HCAPLUS
CN 1-Oxaspiro[2.5]octane-2-carboxylic acid, 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]- (9CI) (CA INDEX NAME)

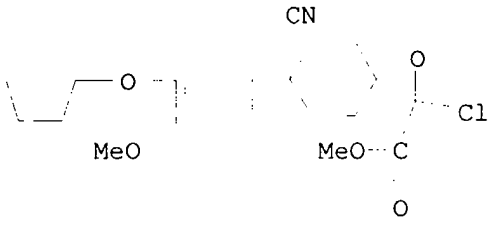


IT **326008-99-5P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(saponification; process for preparing substituted cyclohexanoic acids via α-chloroepoxy esters)

RN 326008-99-5 HCAPLUS

CN 1-Oxaspiro[2.5]octane-2-carboxylic acid, 2-chloro-6-cyano-6-[3-(cyclopentyloxy)-4-methoxyphenyl]-, methyl ester (9CI) (CA INDEX NAME)



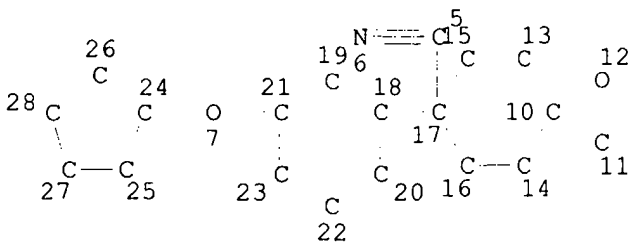
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> d his ful

     FILE 'REGISTRY' ENTERED AT 14:53:21 ON 10 NOV 2003
L1                STR L***
L2              0 SEA SSS SAM L1
L3                STR L1
L4              0 SEA SSS SAM L3
L5                STR L3
L6              0 SEA SSS SAM L5
L7              8 SEA SSS FUL L5
L8              4 SEA ABB=ON  L7 AND N=1 limited to 1 nitrogen
L9                SCREEN 2021 — screen for sulfur, deleted below
L10             7 SEA SSS FUL L5 NOT L9
L11             3 SEA ABB=ON  L10 AND N=1 3 hits in Registry - see "Hcaplus"

     FILE 'HCAPLUS' ENTERED AT 14:57:37 ON 10 NOV 2003
L12             2 SEA ABB=ON  L11  2 cits from CA Plus
```

```
=> d que stat l12
L5                STR
```



```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L9                SCR 2021
L10           7 SEA FILE=REGISTRY SSS FUL L5 NOT L9
L11           3 SEA FILE=REGISTRY ABB=ON  L10 AND N=1
L12           2 SEA FILE=HCAPLUS ABB=ON  L11
```